FIG. 1

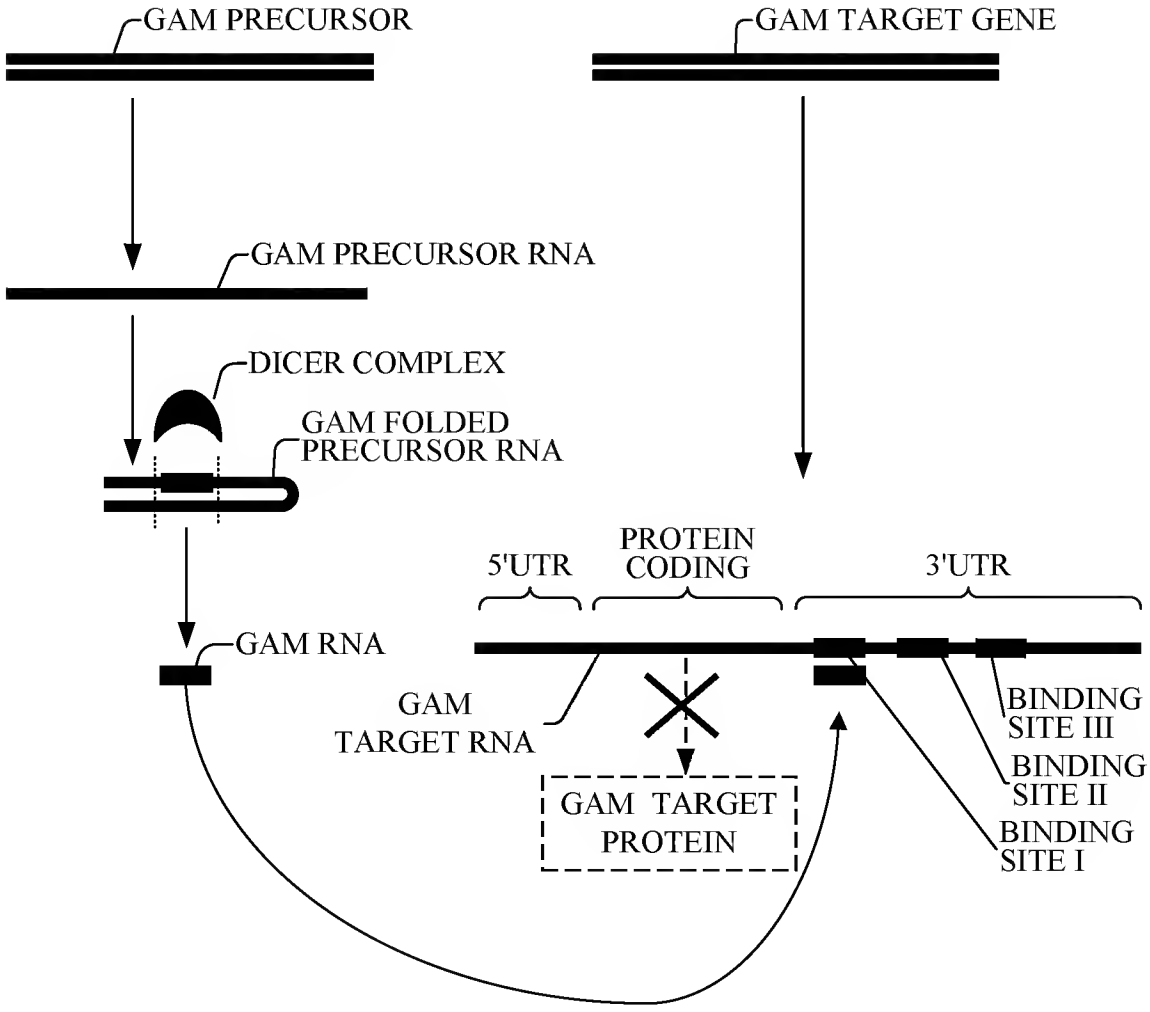

GAM PRECURSOR
GAM TARGET GENE
GAM PRECURSOR RNA
DICER COMPLEX
GAM FOLDED
PRECURSOR RNA
5'UTR
PROTEIN
CODING
3'UTR
GAM RNA
GAM
TARGET RNA
GAM TARGET
PROTEIN
BINDING
SITE III
BINDING
SITE II
BINDING
SITE I

FIG. 2

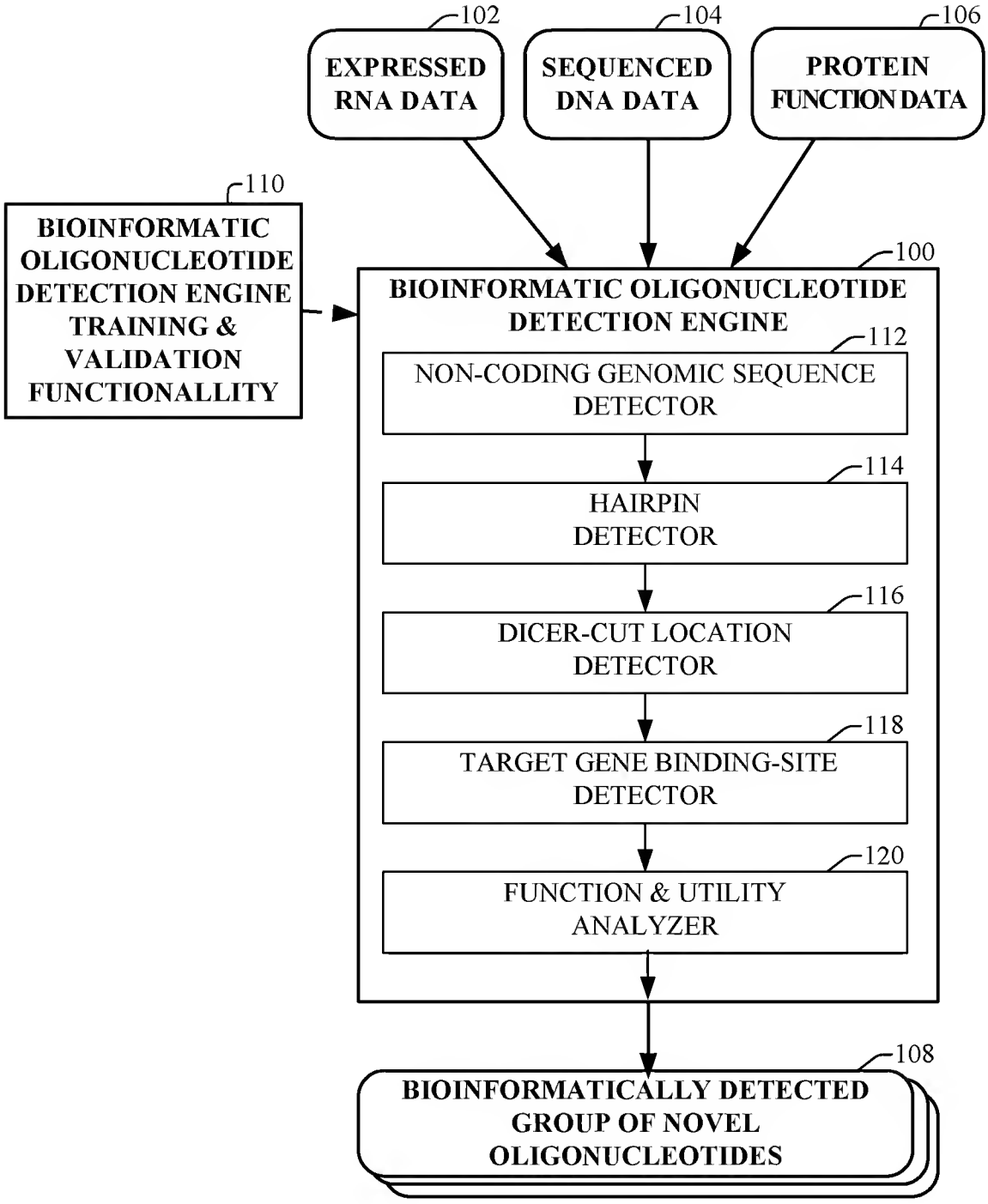

102
EXPRESSED RNA DATA
104
SEQUENCED DNA DATA
106
PROTEIN FUNCTION DATA
110
BIOINFORMATIC OLIGONUCLEOTIDE DETECTION ENGINE TRAINING & VALIDATION FUNCTIONALLITY
100
BIOINFORMATIC OLIGONUCLEOTIDE DETECTION ENGINE
112
NON-CODING GENOMIC SEQUENCE DETECTOR
114
HAIRPIN DETECTOR
116
DICER-CUT LOCATION DETECTOR
118
TARGET GENE BINDING-SITE DETECTOR
120
FUNCTION & UTILITY ANALYZER
108
BIOINFORMATICALLY DETECTED GROUP OF NOVEL OLIGONUCLEOTIDES

FIG. 3

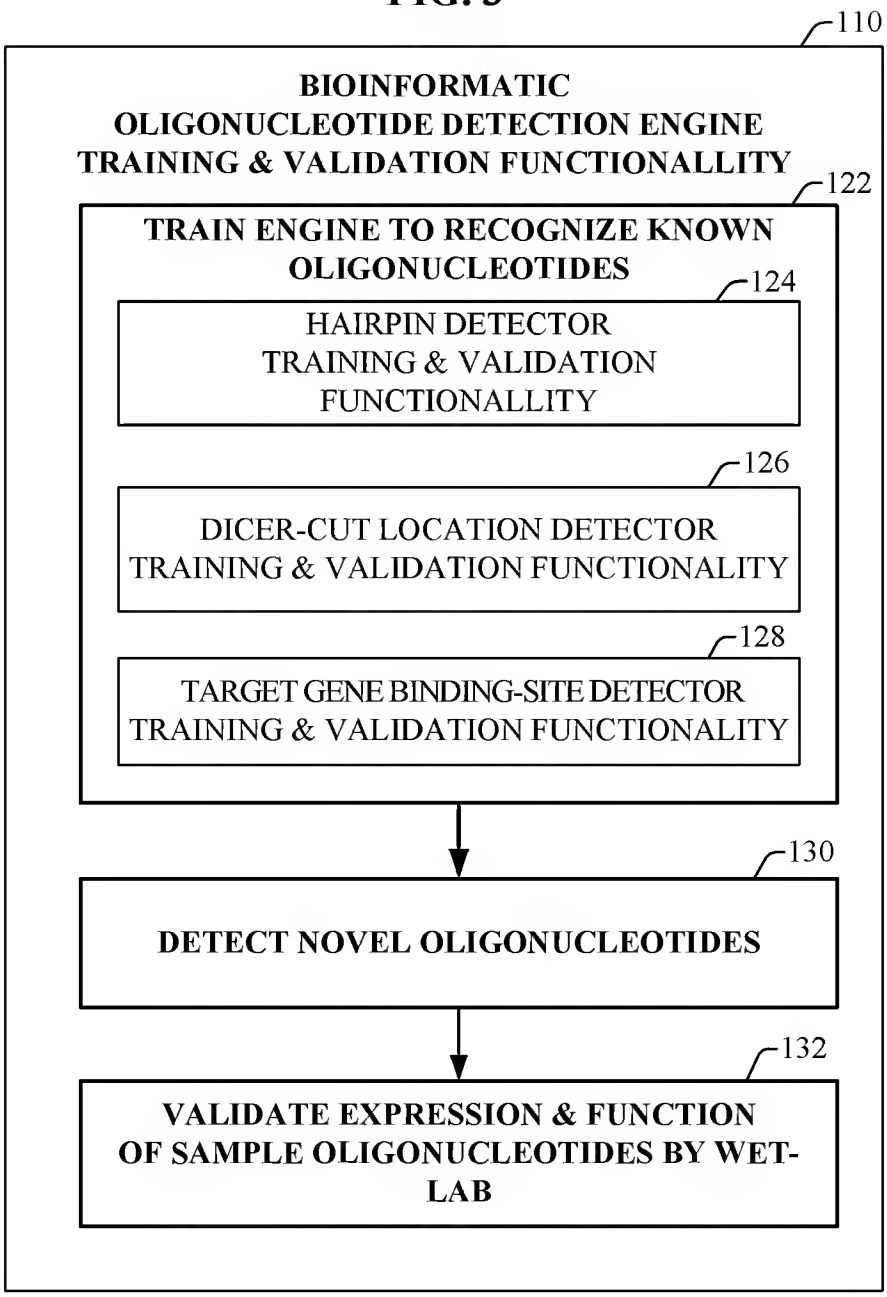

110
BIOINFORMATIC OLIGONUCLEOTIDE DETECTION ENGINE TRAINING & VALIDATION FUNCTIONALLITY
122
TRAIN ENGINE TO RECOGNIZE KNOWN OLIGONUCLEOTIDES
124
HAIRPIN DETECTOR TRAINING & VALIDATION FUNCTIONALLITY
126
DICER-CUT LOCATION DETECTOR TRAINING & VALIDATION FUNCTIONALITY
128
TARGET GENE BINDING-SITE DETECTOR TRAINING & VALIDATION FUNCTIONALITY
130
DETECT NOVEL OLIGONUCLEOTIDES
132
VALIDATE EXPRESSION & FUNCTION OF SAMPLE OLIGONUCLEOTIDES BY WET-LAB

FIG. 4A

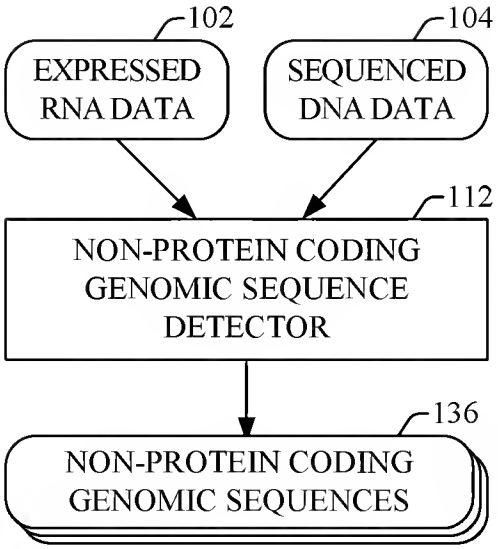

102
104
EXPRESSED RNA DATA
SEQUENCED DNA DATA
112
NON-PROTEIN CODING GENOMIC SEQUENCE DETECTOR
136
NON-PROTEIN CODING GENOMIC SEQUENCES

FIG. 4B

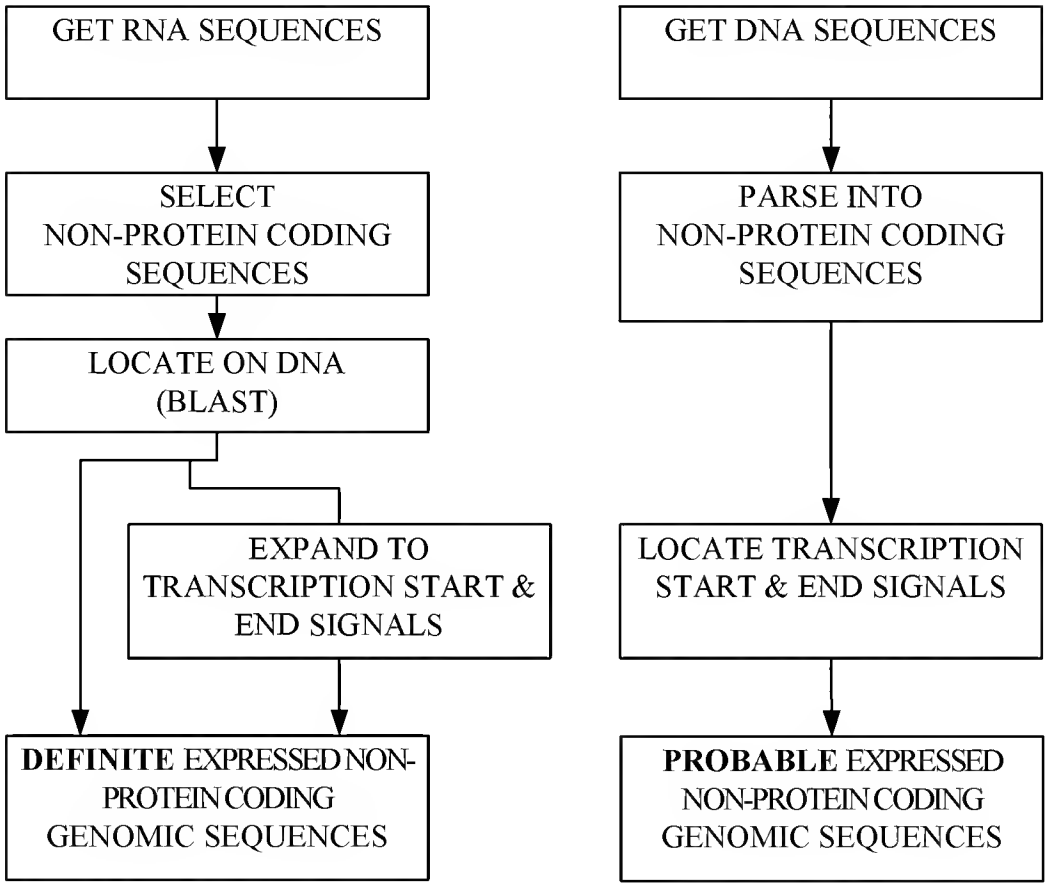

GET RNA SEQUENCES
SELECT NON-PROTEIN CODING SEQUENCES
LOCATE ON DNA (BLAST)
EXPAND TO TRANSCRIPTION START & END SIGNALS
DEFINITE EXPRESSED NON-PROTEIN CODING GENOMIC SEQUENCES
GET DNA SEQUENCES
PARSE INTO NON-PROTEIN CODING SEQUENCES
LOCATE TRANSCRIPTION START & END SIGNALS
PROBABLE EXPRESSED NON-PROTEIN CODING GENOMIC SEQUENCES

FIG. 5A

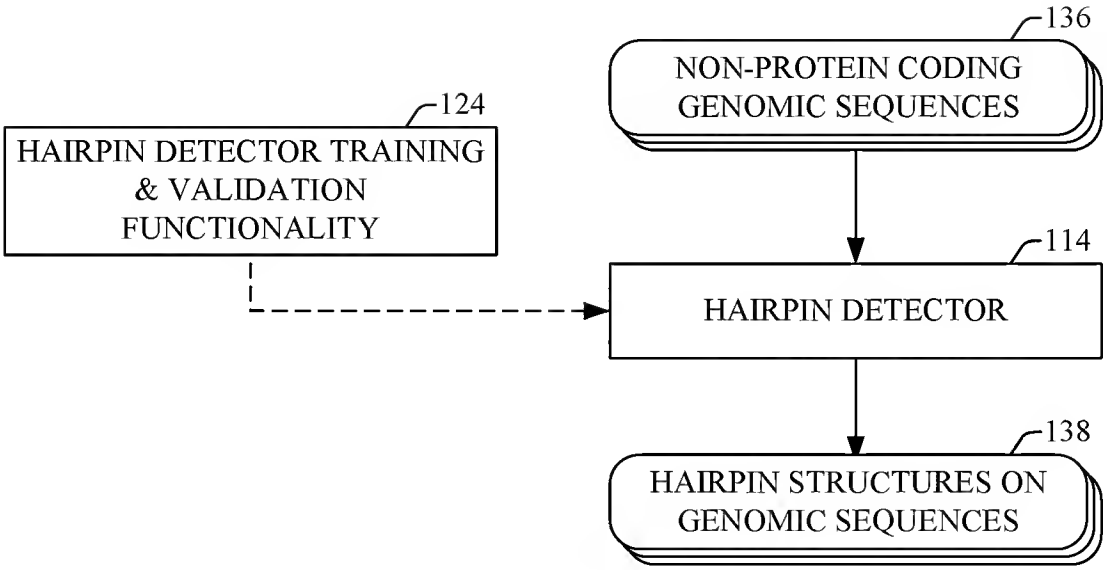

136
NON-PROTEIN CODING GENOMIC SEQUENCES
124
HAIRPIN DETECTOR TRAINING & VALIDATION FUNCTIONALITY
114
HAIRPIN DETECTOR
138
HAIRPIN STRUCTURES ON GENOMIC SEQUENCES

FIG. 5B

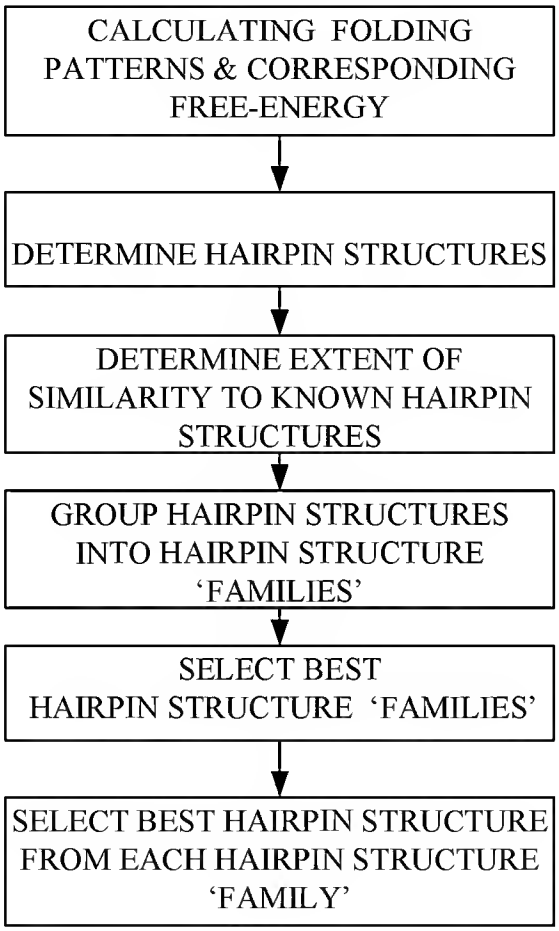

CALCULATING FOLDING PATTERNS & CORRESPONDING FREE-ENERGY
DETERMINE HAIRPIN STRUCTURES
DETERMINE EXTENT OF SIMILARITY TO KNOWN HAIRPIN STRUCTURES
GROUP HAIRPIN STRUCTURES INTO HAIRPIN STRUCTURE 'FAMILIES'
SELECT BEST HAIRPIN STRUCTURE 'FAMILIES'
SELECT BEST HAIRPIN STRUCTURE FROM EACH HAIRPIN STRUCTURE 'FAMILY'

FIG. 6A

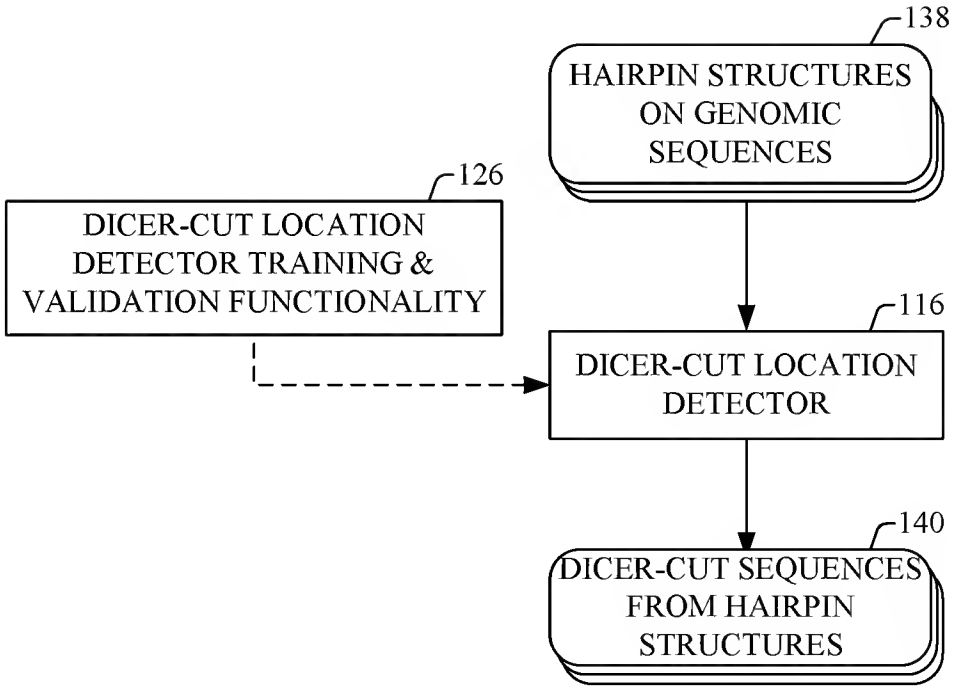

138
HAIRPIN STRUCTURES ON GENOMIC SEQUENCES
126
DICER-CUT LOCATION DETECTOR TRAINING & VALIDATION FUNCTIONALITY
116
DICER-CUT LOCATION DETECTOR
140
DICER-CUT SEQUENCES FROM HAIRPIN STRUCTURES

FIG. 6B

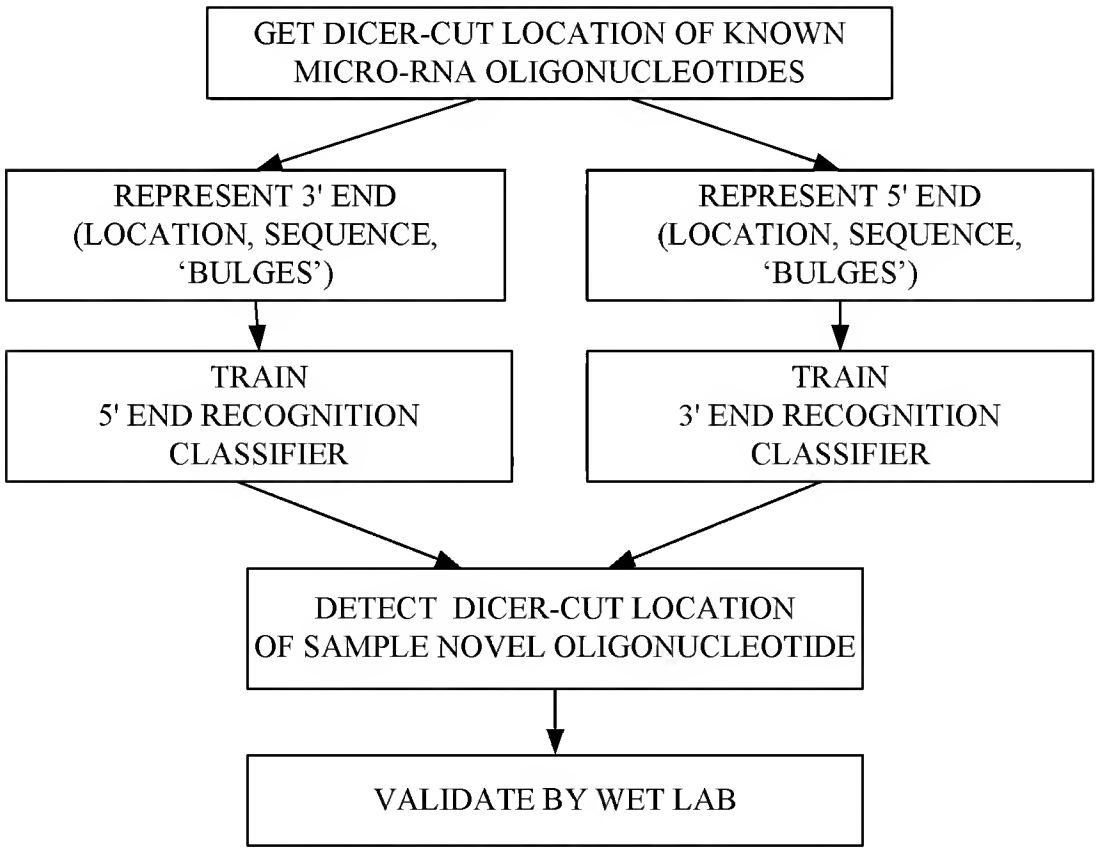

GET DICER-CUT LOCATION OF KNOWN MICRO-RNA OLIGONUCLEOTIDES
REPRESENT 3' END (LOCATION, SEQUENCE, 'BULGES')
REPRESENT 5' END (LOCATION, SEQUENCE, 'BULGES')
TRAIN 5' END RECOGNITION CLASSIFIER
TRAIN 3' END RECOGNITION CLASSIFIER
DETECT DICER-CUT LOCATION OF SAMPLE NOVEL OLIGONUCLEOTIDE
VALIDATE BY WET LAB

FIG. 6C

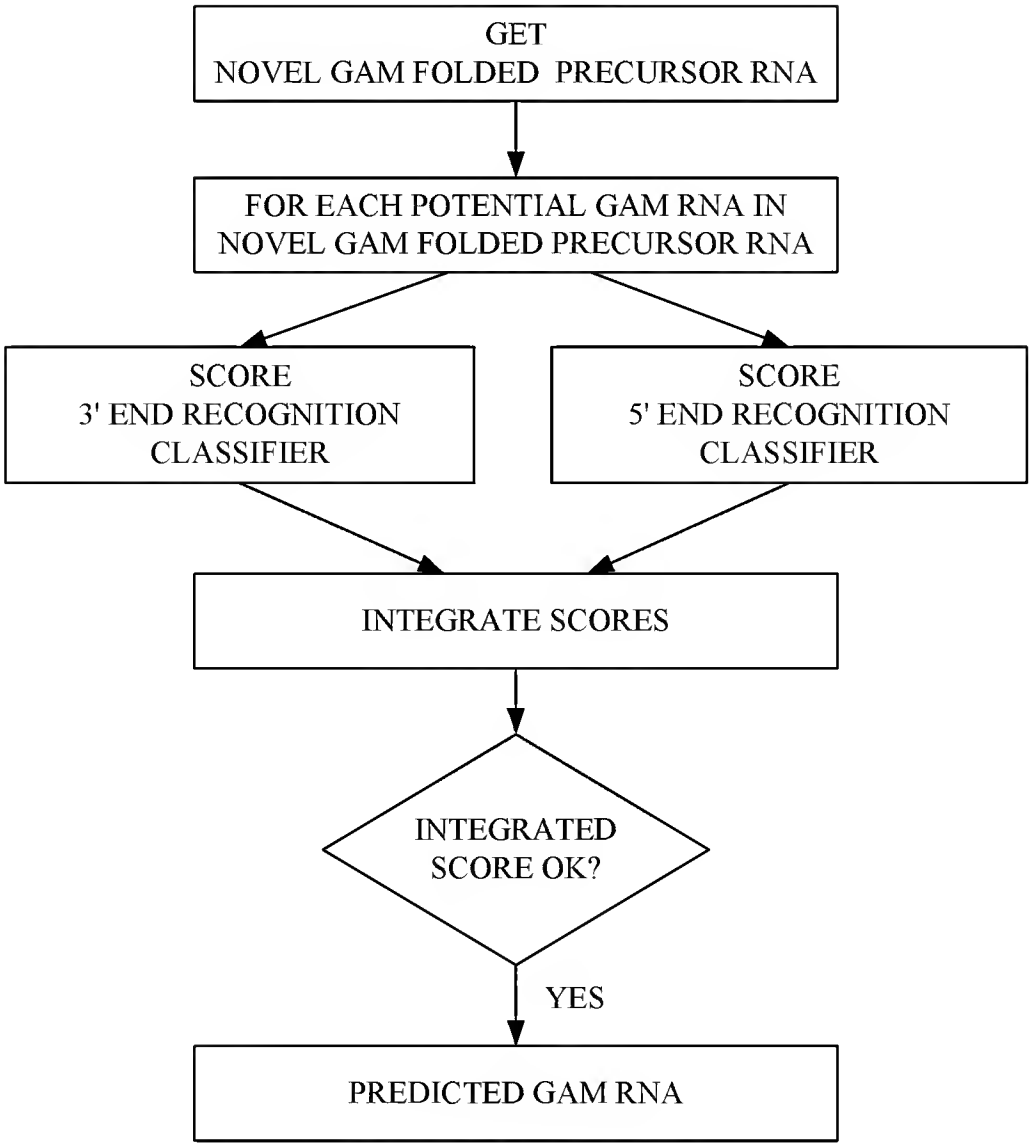

GET
NOVEL GAM FOLDED PRECURSOR RNA
FOR EACH POTENTIAL GAM RNA IN
NOVEL GAM FOLDED PRECURSOR RNA
SCORE
3' END RECOGNITION
CLASSIFIER
SCORE
5' END RECOGNITION
CLASSIFIER
INTEGRATE SCORES
INTEGRATED
SCORE OK?
YES
PREDICTED GAM RNA

FIG. 7A

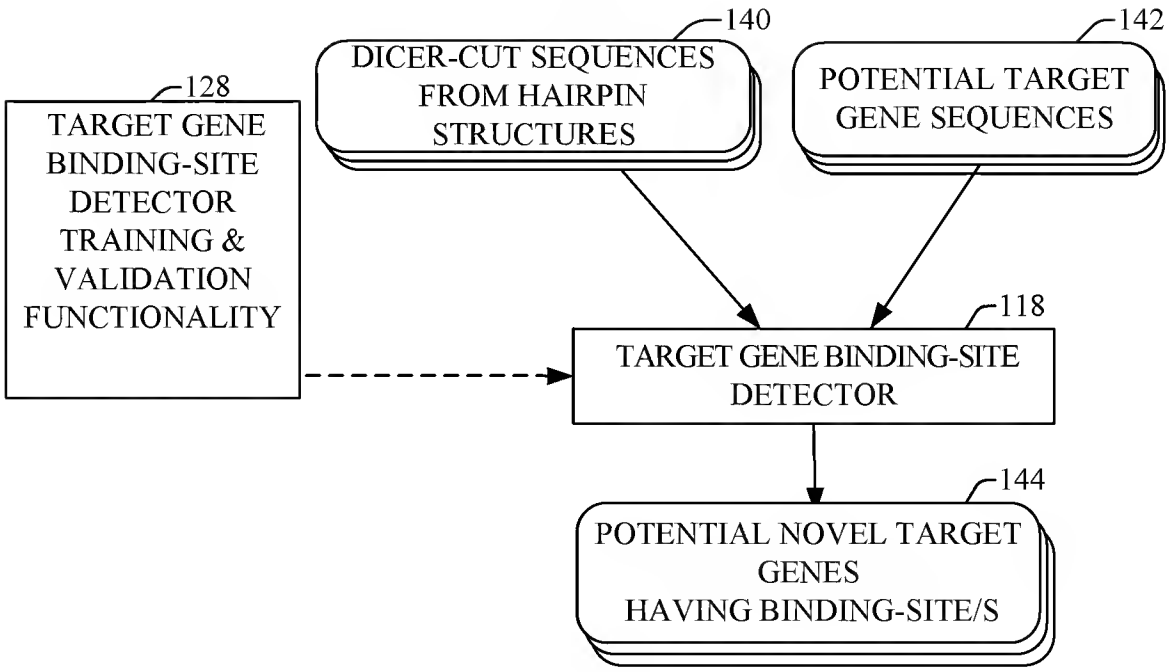

140
DICER-CUT SEQUENCES FROM HAIRPIN STRUCTURES
142
POTENTIAL TARGET GENE SEQUENCES
128
TARGET GENE BINDING-SITE DETECTOR TRAINING & VALIDATION FUNCTIONALITY
118
TARGET GENE BINDING-SITE DETECTOR
144
POTENTIAL NOVEL TARGET GENES HAVING BINDING-SITE/S

FIG. 7B

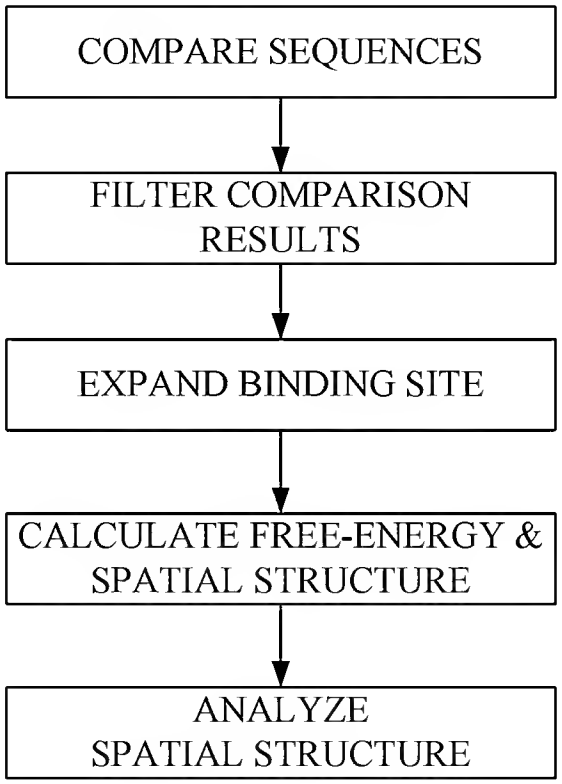

COMPARE SEQUENCES
FILTER COMPARISON RESULTS
EXPAND BINDING SITE
CALCULATE FREE-ENERGY & SPATIAL STRUCTURE
ANALYZE SPATIAL STRUCTURE

FIG. 8

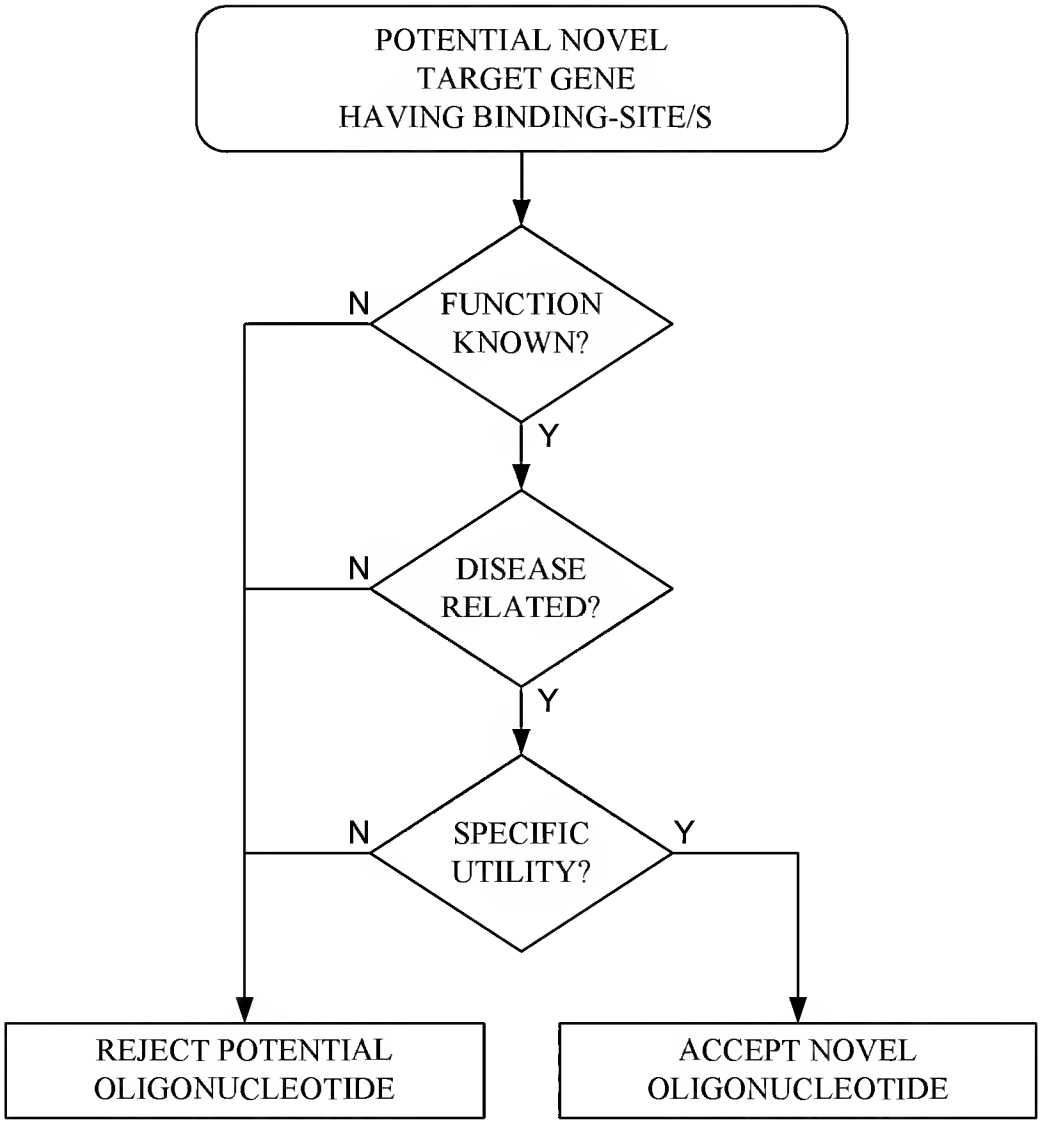

POTENTIAL NOVEL
TARGET GENE
HAVING BINDING-SITE/S
FUNCTION
KNOWN?
N
Y
DISEASE
RELATED?
N
Y
SPECIFIC
UTILITY?
N
Y
REJECT POTENTIAL
OLIGONUCLEOTIDE
ACCEPT NOVEL
OLIGONUCLEOTIDE

FIG. 9

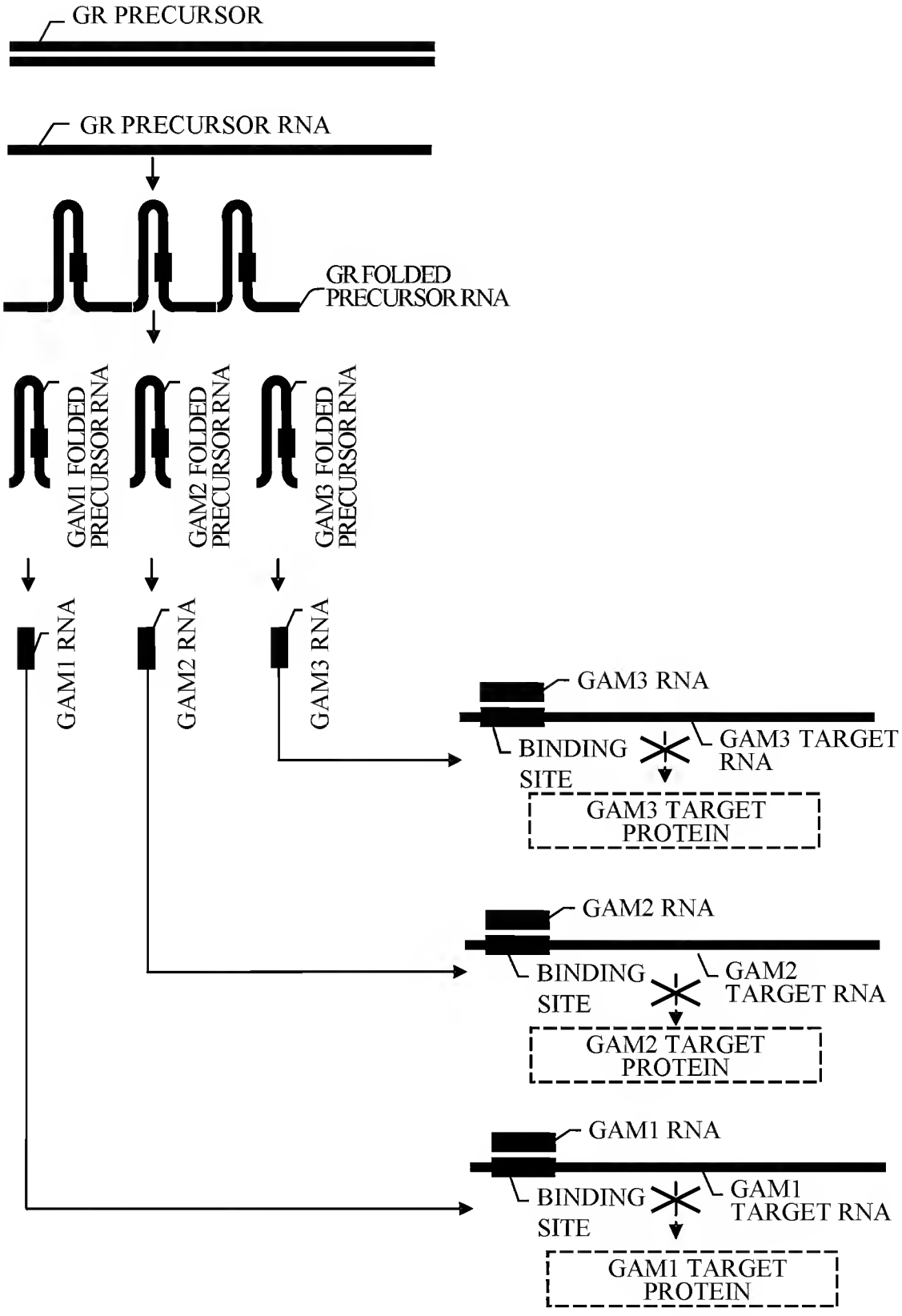

GR PRECURSOR
GR PRECURSOR RNA
GR FOLDED PRECURSOR RNA
GAM1 FOLDED PRECURSOR RNA
GAM2 FOLDED PRECURSOR RNA
GAM3 FOLDED PRECURSOR RNA
GAM1 RNA
GAM2 RNA
GAM3 RNA
GAM3 RNA
BINDING SITE
GAM3 TARGET RNA
GAM3 TARGET PROTEIN
GAM2 RNA
BINDING SITE
GAM2 TARGET RNA
GAM2 TARGET PROTEIN
GAM1 RNA
BINDING SITE
GAM1 TARGET RNA
GAM1 TARGET PROTEIN

FIG. 10

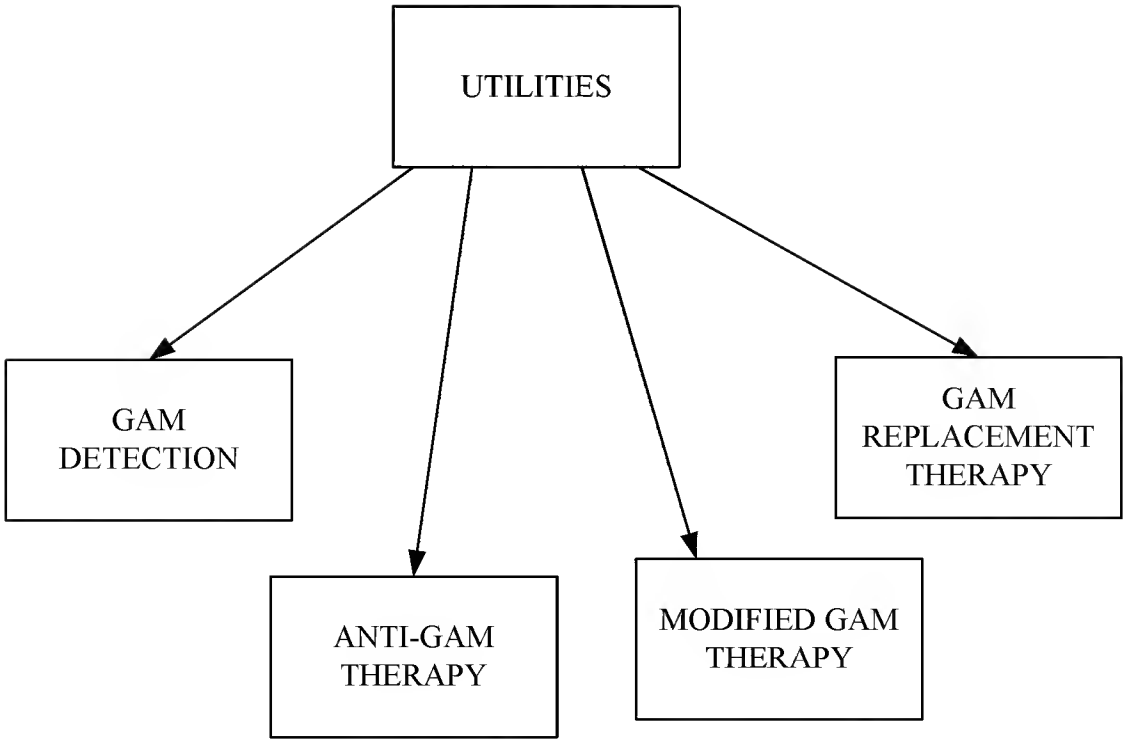

UTILITIES
GAM DETECTION
ANTI-GAM THERAPY
MODIFIED GAM THERAPY
GAM REPLACEMENT THERAPY

FIG. 11A

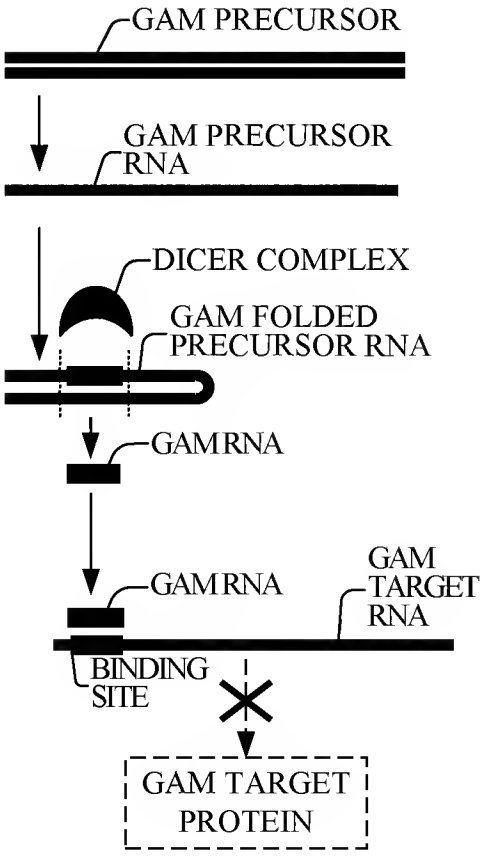


FIG. 11B

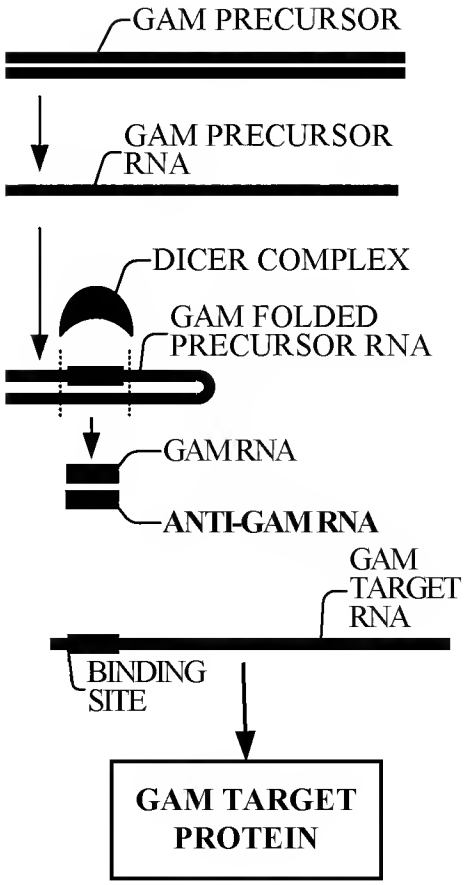


FIG.12A

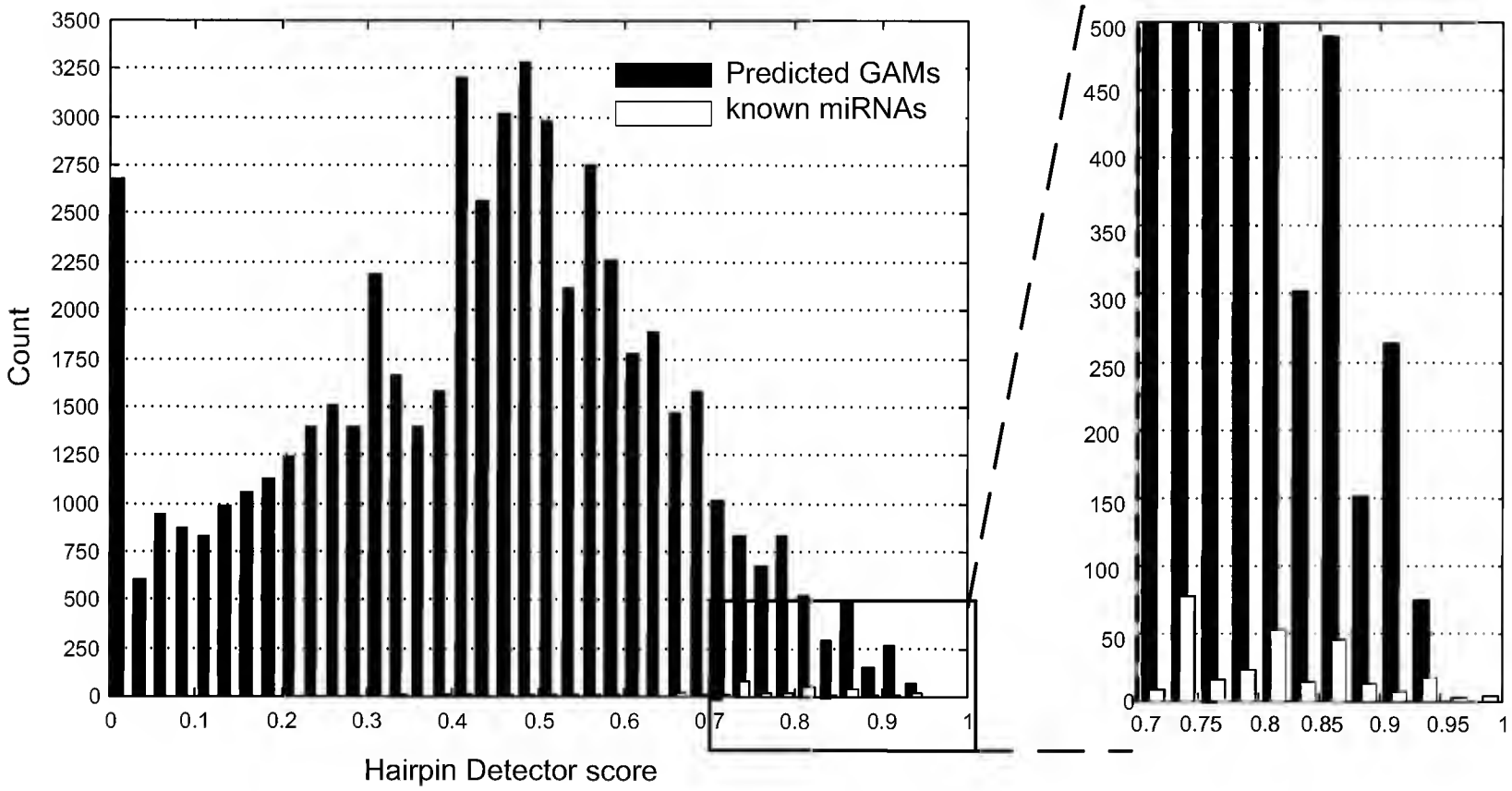

Predicted GAMs
known miRNAs
Count
Hairpin Detector score
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
500
450
400
350
300
250
200
150
100
50
0
0.7
0.75
0.8
0.85
0.9
0.95
1

FIG. 12B

GAM Detection Group	Published Hairpins Detection	Background Hairpins Filtering	Lab Validation of Human GAMs		
			Sent	Positive	% Success
A	382	~2850000 (95 %)	101	37	37%
Overall	440	~3000000	168	52	31%

FIG. 13A

KNOWN MIRS

PREDICTED GAM OLIGONUCLEOTIDES:

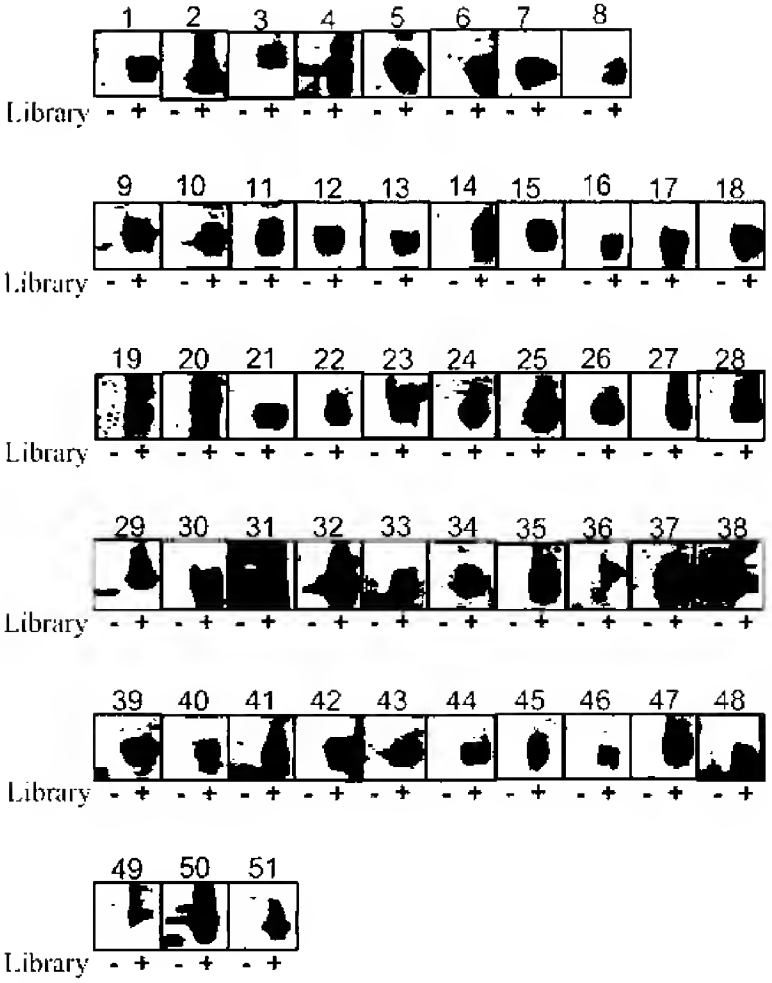


FIG. 13B

NUMBER	NAME	SEQUENCE (5 TO 3)	SEQUENCED
1	hsa-miR-21	TAGCTTATCAGACTGATGTTGA	+
2	hsa-miR-27b	TTCACAGTGGCTAAGTTCTGCA	+
3	hsa-miR-186	AAAGAATTCTCCTTTTGGGCTT	+
4	hsa-miR-93	AAGTGCTGTTCGTGCAGGTAGT	+
5	hsa-miR-26a	TCAAGTAATCCAGGATAGGCTG	+
6	hsa-miR-191	AACGGAATCCCAAAAGCAGCTG	+
7	hsa-miR-31	GGCAAGATGCTGGCATAGCTGT	+
8	hsa-miR-92	TATTGCACTTGTCCCGGCCTGT	+
9	GAM3418-A	ATCACATTGCCAGGGATTACCA	+
10	GAM4426-A	GAAGTTTGAAGCCTGTTGTTCA	+
11	GAM281-A	CACTGCACTCCAGCCTGGGCAA	
12	GAM7553-A	TAGGTAGTTTCCTGTTGTTGGG	+
13	GAM5385-A	TCACAGTGAACCGGTCTCTTTC	+
14	GAM2608-A	TAAGGTGCATCTAGTGCAGTTA	
15	GAM1032-A	CTAGACTGAAGCTCCTTGAGGA	+
16	GAM3431-A	TAATACTGCCGGGTAATGATGG	
17	GAM7933-A	TAGCAGCACATAATGGTTTGAA	
18	GAM3298-A	AAAGTGCTCATAGTGCAGGTAG	+
19	GAM7080-A	TTTCCACAGCGGCCAATTCTTC	+
20	GAM895-A	AGCTGCCAGTTGAAGAACATTT	
21	GAM3770-A	AAGTTAAGAGCTCCCAGGCCTG	
22	GAM337162-A	ACTGCACTCCAGCCTGGGCAAC	+
23	GAM8678-A	GTGTTCCAGGAAGTCGTCTTGA	
24	GAM2033-A	TCAAGCTCATTCCTCTAACCTC	
25	GAM7776-A	CATTGCACTCCAGCCTGGGCAA	+
26	GAM8145-A	ACATGATCTCCTCACTCTAGGA	
27	GAM25-A	AATTGCTTGAACCCAGGAAGTG	+
28	GAM7352-A	TGTTTAAGTAGCTTATTTATCT	
29	GAM337624-A	TCTAAGAGAAAGGAAGTTCAGA	+
30	GAM1479-A	GAAGGCAGTAGGTTGTATAGTT	+
31	GAM2270-A	ATCACATTGCCAGTGATTACCC	+
32	GAM7591-A	TTGGAGTAATTCAGTATAGGTT	+
33	GAM8285-A	AGTAGACAGTGGCAACATAGTC	
34	GAM6773-A	CTAGCCTGTTTGTCCTCACCCC	+
35	GAM336818-A	TGAGGTGGGATCCCGAGGCC	+
36	GAM336487-A	TGGCTAGGTAAGGGAAG	+
37	GAM337620-A	AATCATCATTATTTTGAAGTTTA	+
38	GAM336809-A	TAAGGCATTTTTATGGT	+
39	GAM5346-A	GCTGTTGTTAAGGGCACTTGGG	
40	GAM8554-A	TTCATGGGAGCAGGTGGTACAG	
41	GAM2701-A	ACTGCACTCCAGTCTGGGTGAC	
42	GAM7957-A	TCACTGCAACCTCTGCCTCCCG	
43	GAM391-A	CAGATCACATCCATCCGTCACC	
44	GAM6633-A	GCACTCAAGCCTGGGTTACAGA	
45	GAM19	AGAGAGTGGCAGGTCTGTTCCT	
46	GAM8358-A	GATGAGGCAGCACTTGGG	
47	GAM3229-A	TGAGGTGGGAGAATTGCTTGAA	
48	GAM7052-A	CATGTAATCCCAGCTACTCAGG	
49	GAM3027-A (mmu-MIR-29c)	TAGCACCATTTGAAATCGGTTA	+
50	GAM21 (mmui-MIR-130b)	CAGTGCAATGATGAAAGGGCAT	+
51	GAM oligonucleotide(mmu-MIR-30e)	TGTAAACATCCTTGACTGGAAG	+

FIG. 14A

FIG. 14B

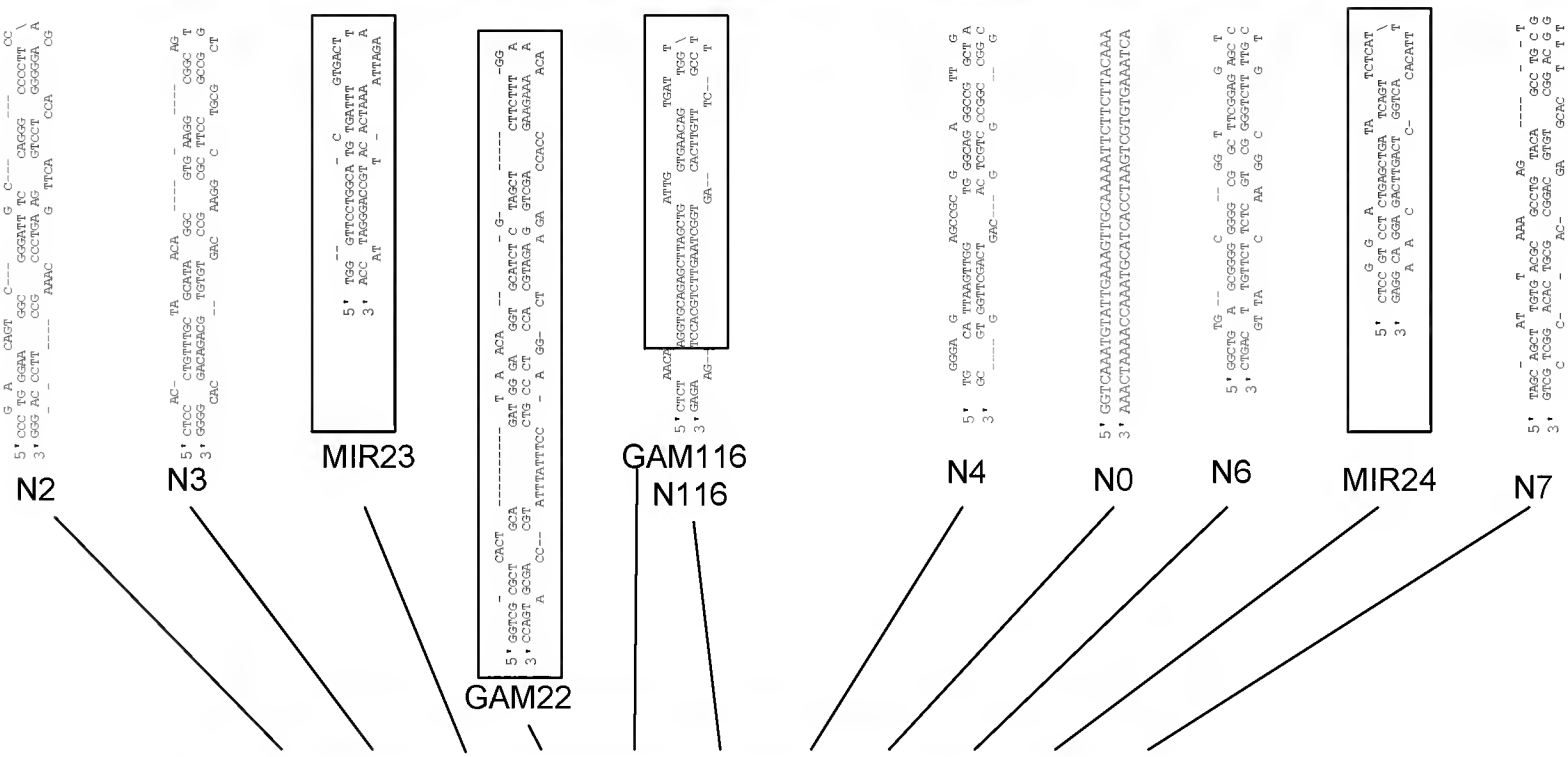


FIG. 14C

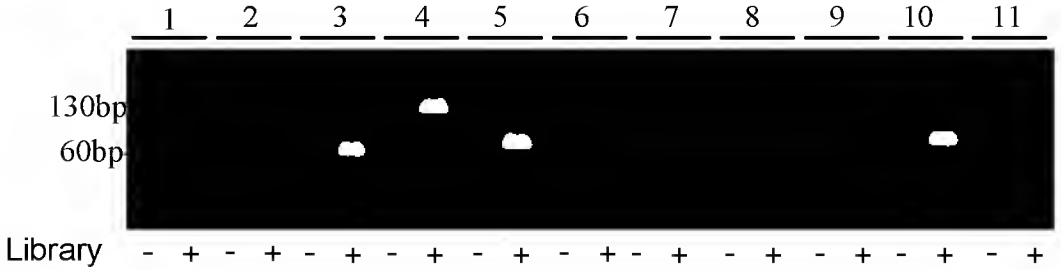


FIG. 15A

EST72223 (705 nt.)

EST72223 sequence:

CCCTTATTAGAGGATTCTGCTCATGCCAGG**GTGAGGTAGTAAGTTGTATTG**
TTGTGGGGTAGGGATATTAGGCCCCAATTAGAAGATAACTATACAACT **MIR98**
TACTACTTTCCCTGGTGTGTGGCATATTCACACTTAGTCTTAGCAGTGTTGCC
TCCATCAGACAAAGTTGTAGATGTTCCTTGGATAATTTGGACTGGAAGAAAAGA
GACATGGAAGGGGACAGATGGTGTTTAGGGTGAGGCAGATGTCATTATAAAGT
GACTTGTCTTTCATTAATTGGAGCATATAATTATTTTACCTTTGGGCATGAACTC
ATTTTGCTATTCTTCAACTGTGTAATGATTGCATTTTATTAGTAATAGAACAGGA
ATGTGTGCAAGGGAATGGAAAGCATACTTTAAGAATTTTGGGCCAGGCGCGGT
GGTTCATGCCTGTAATCCCAGCATTTTTGGGAGGCCGAGGCGGGTGGATCAC
CTGAGGTCAGGAGTTCGAGACCAACCTGGCCAACACGGCGAAACCCCGCCTC
TACTCAAATACAAAAATTAGCCAGGCTTGGTGACACTCGCCTGTGGTCCCAGC
TACTCAGGAGGCT**GAGGCAGGAG**AATTGCTTGAACCCAGGAAGTGGAG **GAM25**
GCTTCAGTGAGCTGAGAACACGCCACTGCACTCCAGTCCTGGGCAAC
AGAGCAAGACTCTGTCTCAGGAAAAAAAAAG

FIG. 15B

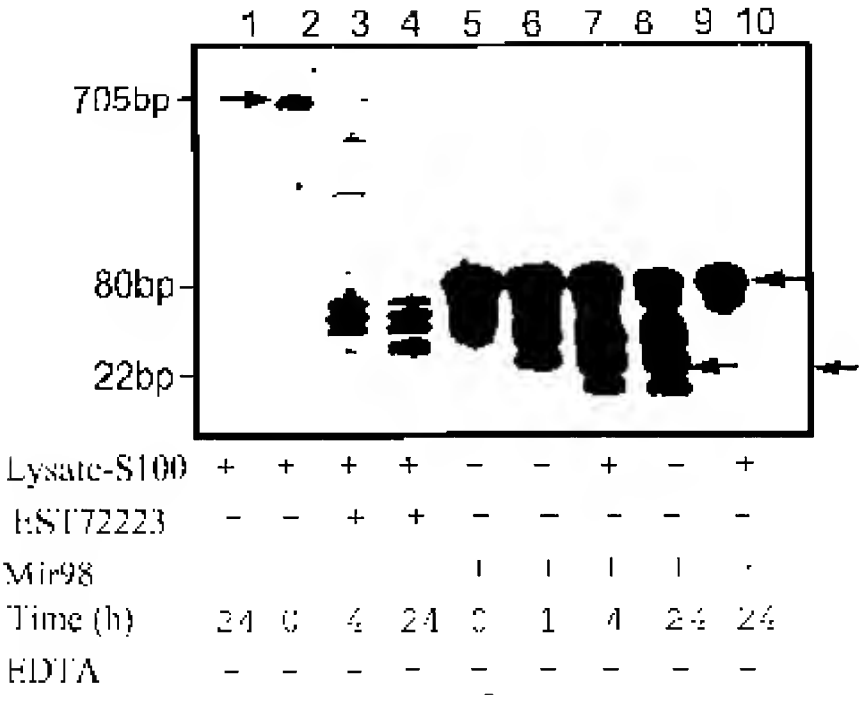
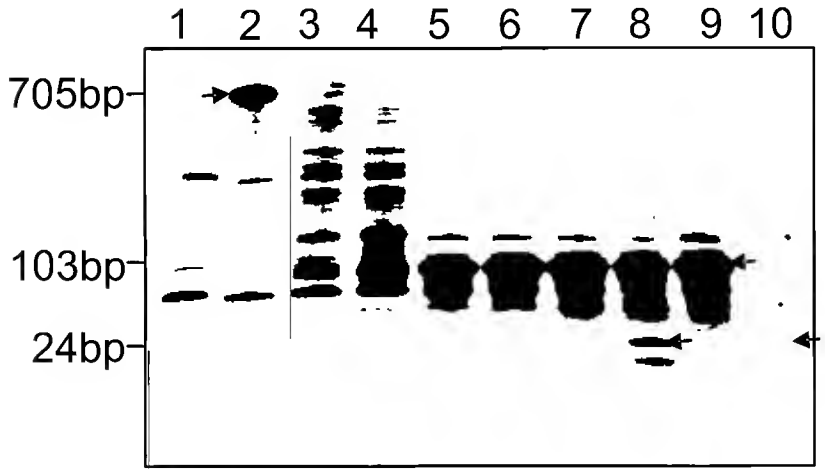
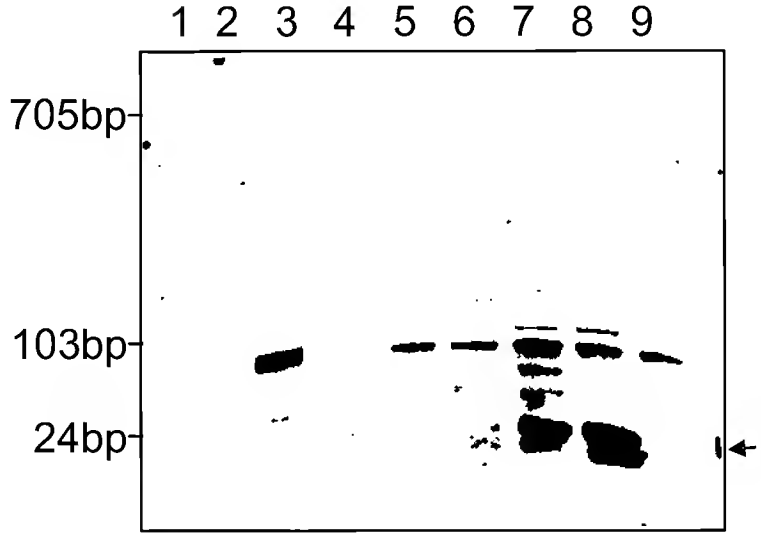


FIG. 15C



Lysate-S100	+	+	+	+	+	+	+	+	+
EST72223	–	+	+	+	–	–	–	–	–
GAM25	–	–	–	–	+	+	+	+	+
Time (h)	24	0	4	24	0	0.5	1	24	24
EDTA	–	–	–	–	–	–	–	–	+

FIG. 15D



Lysate-S100	+	+	+	+	+	+	+	+	+
EST72223	–	+	+	+	–	–	–	–	–
GAM25	–	–	–	–	+	+	+	+	+
Time (h)	24	0	4	24	0	0.5	1	24	24
EDTA	–	–	–	–	–	–	–	–	+

FIG. 16A

5'UTR SEQUENCE (5' TO 3') OF HIV-1(U5-R)

G<u>**GTCTCTCTGGTTAGACCAGATC**</u>**TGAGCCTGGGAGCTCTCTGGCTAACT**
AGGGAACCCCACTGCTTAAGCCTCAATAAAGCTTGCCTTGAGTGCTTCAAGTA
GTGTGTGCCCGTCTGTTGTGTGACTCTGGTAACTAGAGATCCCTCAGACCCTT
TTAGTCAGTGTGGAAAATCTCTAGCAGTGGCGCCCGAACAGGGACCTGAAAG
CGAAAGGGAAACCAGAGGAGCTCTCTCGA**CGCAGGACTCGGCTTGCTGAA**
GCGCGCACG<u>**GCAAGAGGCGAGGGGCG**</u>GCGACTGGTGAGTACGCCAAAAA
TTTTGACTAGCGGAGGCTAGAAGGAGAGAG

FIG. 16B

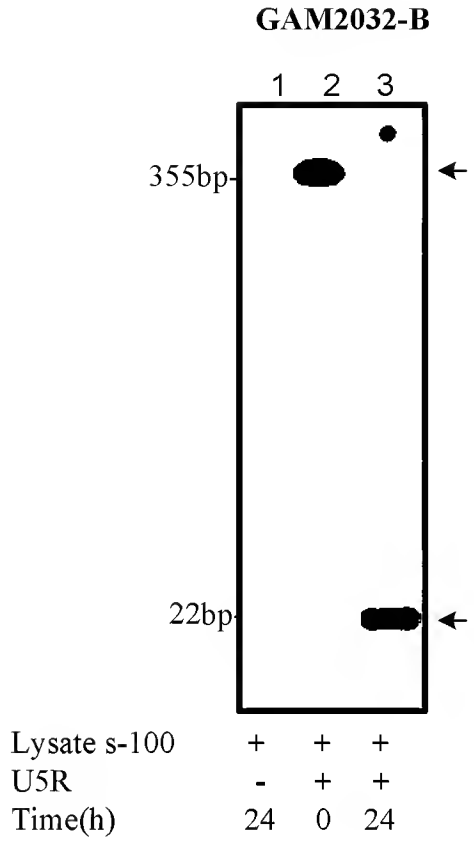


FIG. 16C

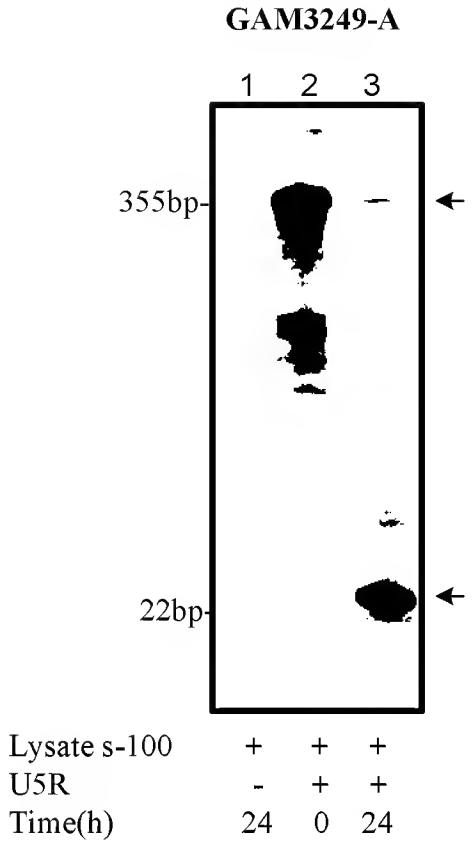


FIG.16D

TRANSCRIPT SEQUENCE (5' TO 3')

ACAGGGCTGCTATTAACAAGAG
ATGGTGGTAATAGCAA**CAATGA**
GTCCGAGATCTTCAGACCTGG
AGGAGGAGATATGAGGGACAA
TTGGAGAAGTGAATTATATAAA
TATAAAGTAGTAAAAATTGAACC
ATTAGGAGTAGCACCCACCAAG
GCAAAGAGAA

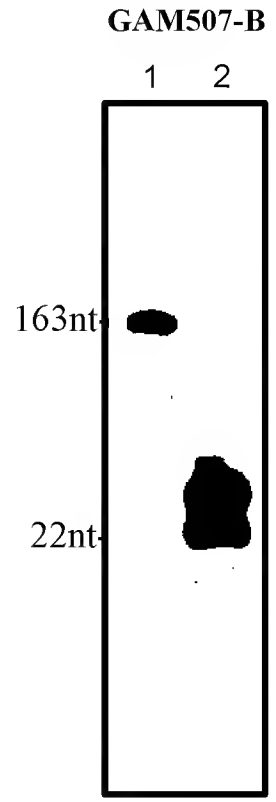


FIG.16E

TRANSCRIPT SEQUENCE (5' TO 3')

TGGGAAGCCCTCAAATATTGGTGG
AATCTCCTACAGTATTGGAGTCAG
GAACTAAAGAATAG**TGCTGTTAG**
CTTGCTCAATGCCACAGCCATAG
CAGTAGCTGAGGGGACAGATAG
GGTTATAGAAGTAGTACAAGGAG
CTTGTAGAGCTATTCGCCACATACC
TAGAAGAATAAGACAGGGCTTGGA
AAGGATTTTGCT